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Unprecedented Catalytic Enantioselective Trapping of Arene Oxides with Dialkylzinc Reagents.

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General. All reactions were conducted in flame dried glassware with magnetic stirring under an atmosphere of argon. Toluene was distilled from sodium/benzophenone ketyl and stored under argon. Et_2Zn (1.1 M solution in toluene) and Me_2Zn (2.0 M solution in toluene) were purchased from Aldrich. Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Silica gel 60 (Macherey-Nagel 230-400 mesh) was used for flash chromatography. Solvents for extraction and chromatography were HPLC grade.

Optical rotation were measured on a Perkin-Elmer 241 digital polarimeter with a 1 dm cell. ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer on $CDCl_3$ solution. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.26). ^{13}C NMR spectra were recorded on a Bruker AC-200 (50 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 77.7). Gas chromatography was performed on a Perkin-Elmer 8420 apparatus (FI detector) using a Chromopak fused silica 25 m x 0.25 mm column, coated with CP-Cyclodextrin-B-236-M-19). In all cases, the injector and detector temperature was 250°C and a 1.8 mL / min helium flow was employed. Analytical high performance liquid chromatography (HPLC) was performed on a Waters 600E equipped with a Waters 990 photodiode array detector using a Daicel Chiralcel OD-H column.

A typical procedure for the enantioselective trapping of arene oxides with dialkylzinc reagents. Formation of 3a (5a).

A 25 ml Schlenk tube under argon was charged with $Cu(OTf)_2$ (5.8 mg, 0.015 mmol), (*R,R,R*)-**2** (16.2 mg, 0.03 mmol), anhydrous toluene (2 ml), and was stirred at room temperature for 40 min. The colorless solution was cooled to -78°C and subsequently additioned with a solution of arene oxide **1a** (94 mg, 1.0 mmol) in toluene (0.5 ml) and Me_2Zn (0.75 ml). The reaction was followed by GC analysis and quenched with saturated aqueous NH_4Cl after 1h (95% conversion). Extraction with Et_2O and evaporation of the dried (Na_2CO_3) organic phase gave a crude product (106 mg) essentially constituted by the two regioisomers **3a** and **5a** in a 69:31 ratio and the chiral ligand (*R,R,R*)-**2**. In our hands, it was not possible to isolate in a pure state the achiral γ-adduct **5a**. However the presence of **5a** as a reaction product was clearly indicated by ^1H and ^{13}C NMR of the mixture. **5a**: ^1H NMR δ ($CDCl_3$): 5.97-5.7 (m, 4H), 4.49-4.37 (m, 1H), 2.72-2.56 (m, 1H), 0.98 (d, 3H, *J* = 7.3 HZ). ^{13}C NMR δ ($CDCl_3$): 127.7, 122.3, 62.6, 38, 21.9. After repeated chromatographic purification (SiO_2, hexanes/Et_2O=85:15 plus 1% NEt_3) it was possible to obtain an analytical pure sample of **3a** (8 mg).

(1*S*, 6*S*)-6-Methyl-2,4-cyclohexadien-1-ol (3a): a colourless liquid. ^1H NMR δ ($CDCl_3$): 5.97-5.70 (m, 4H), 3.97-3.87 (m, 1H), 2.52-2.33 (m, 1H), 0.96 (d, 3H, *J* = 7.3 Hz). ^{13}C NMR δ ($CDCl_3$): 134.2, 133.4, 127.2, 125.4, 71.4, 31.5, 17.8.

The enantiomeric excess of **3a** (93%) was determined by chiral GC (CP-cyclodex-β-column), isothermal 107 °C, (1*S*, 6*R*) (minor) t_R14.2 min, (1*R*, 6*S*) (major) t_R 14.7 min.

Absolute configuration of **3a** was determined by comparison of optical rotation after conversion (H_2/Pd/AcOEt on charcoal) into *trans*-2-methylcyclohexanol, a compound of known absolute configuration.[1]

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[1] M.P. Doyle, A.V. Kalinin, D.G. Ene *J. Am. Chem. Soc.* 1996, ***118***, 8837.

(1*S*, 6*S*)-(+)-6-Methyl-2,4-cyclohexadien-1-benzoate (3a-Bz): to a solution of a 64:36 mixture of **3a** and **5a** (40 mg, 0.36 mmol) in CH_2Cl_2 (2ml) and pyridine (0.5 ml), benzoyl chloride (41 μl, 0.65 mmol) was added at 0°C under stirring. The mixture was kept at 0°C for 2 h, allowed stand at room temperature for 24h, and then quenched at 0°C with H_2O maintaining the stirring for further 2h. The solution was then diluted with CH_2Cl_2, washed with water, NH_4Cl saturated solution, NaCl saturated solution and dried over $MgSO_4$. Only benzoylated **3a** was found as a product and the crude reaction mixture was purified by flash chromatography (hexanes: AcOEt=85:15) to deliver **3a-Bz** (39 mg, 80% yield). $[\alpha]_D^{23}$=+267.3 (*c*=2.75, CH_2Cl_2), ^{1}HNMR ($CDCl_3$): 8.08-8.01 (m, 2H), 7.58-7.38 (m, 3H), 6.18-6.11 (m, 1H), 6.03-5.84 (m, 3H), 5.43 (t, 1H, *J* = 5.1 Hz), 2.81-2.64 (m, 1H), 1.1 (d, 3H, *J* = 7.36 Hz). ^{13}CNMR: 166.9, 133.5, 133.4, 131.3, 130.3, 129.2, 127.7, 122.9, 122.3, 74.1, 34.8, 17.6. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.35; H, 6.53.

(1*S*, 6*S*)-6-Ethyl-2,4-cyclohexadien-1-ol (4a): Following the typical procedure $Cu(OTf)_2$ (11.6 mg, 0.03 mmol), (*R,R,R*)-**2** (32.4 mg, 0.06 mmol), arene oxide **1a** (188 mg, 2.0 mmol), Et_2Zn (2.7 ml), 1h at –78°C (95% conversion), afforded after the usual work-up a crude reaction mixture (248 mg) constituted by the regioisomers **4a** and **6a** in a 38:62 ratio and the chiral ligand (*R,R,R*)-**2**. After repeated chromatographic purifications (SiO_2, hexanes/Et_2O=85:15 plus 1% NEt_3) it was possible to obtain an analytical pure sample of **4a** (15 mg), a colorless liquid; ^{1}H NMR δ ($CDCl_3$): 5.97-5.71 (m, 4H), 4.03-3.94 (m, 1H), 2.35-2.21 (m, 1H), 1.46-1.28 (m, 2H), 0.89 (t, 3H, *J* = 7.4 Hz).^{13}C NMR δ ($CDCl_3$): 132.2, 131.5, 127.6, 125.4, 69.1, 44.6, 25.4, 12.0. It was not possible to isolate in a pure state the achiral γ-adduct **6a**. However the presence of **6a** as a reaction product was clearly indicated by ^{1}H and ^{13}C NMR of the mixture. **6a**: ^{1}H NMR δ ($CDCl_3$): 5.97-5.71 (m, 4H), 4.47-4.38 (m, 1H), 2.65-2.52 (m, 1H), 1.46-1.28 (m, 2H), 0.77 (t, 3H, *J* = 7.4 Hz). The enantiomeric excess of **4a** (64%)

was determined by chiral GC (CP-cyclodex-β-column), isothermal 107 °C, (1*S*, 6*R*) (minor) t_R22.3 min, (1*R*, 6*S*) (major) t_R 22.8 min.

Bicyclo [4.3.0]-2-methyl-nona-3,5-dien-1-ol (3b): Following the typical procedure $Cu(OTf)_2$ (13 mg, 0.034 mmol), (*R*,*R*,*R*)-**2** (36.3 mg, 0.067 mmol), arene oxide **1b** (300 mg, 2.24 mmol), Me_2Zn (1.7 ml), 3h at –78°C (ca. 95% conversion), afforded after the usual work-up a crude reaction mixture (280 mg) constituted by the regioisomer **3b** and **5b** in a 80:20 ratio and the chiral ligand (*R*,*R*,*R*)-**2**. Chromatographic purification (SiO_2, hexanes/Et_2O=80:20 plus 1% NEt_3) afforded pure **3b** (80 mg, 24%) as a colourless liquid. R_f=0.38 (hexanes/Et_2O=8:2); $[\alpha]_D^{23}$=-427.7 (*c*=1.77, MeOH). ^{1}H NMR δ (C_6D_6): 5.78 (dd, 1H, *J* = 9.3 and 5.2 Hz), 5.62-5.49 (m, 2H), 2.62-2.40 (m, 1H), 2.11-1.75 (m, 4H), 1.59-1.43 (m, 2H), 0.71 (d, 3H, *J* = 7.3 Hz). ^{13}C NMR δ (C_6D_6): 147.0, 131.0, 122.5, 116.0, 79.4, 40.3, 35.7, 30.5, 23.2, 15.5.

The enantiomeric excess of **3b** (≥95%, not baseline separation) was determined at 220 nm by chiral HPLC (Daicel Chiralcel OD-H column), hexanes / 2-propanol 99:1, flow rate 0.5 mL/min, (-) t_R10.9, (+) t_R 11.5 min.

Following the typical procedure $Cu(OTf)_2$ (13 mg, 0.034 mmol), (*R*,*R*,*R*)-**2** (36.3 mg, 0.067 mmol), arene oxide **1b** (300 mg, 2.24 mmol), Et_2Zn (3.1 ml), 3h at –78°C (95% conversion), afforded after the usual work-up a crude reaction mixture (320 mg) constituted by the regioisomer **4b** and **6b** in a 78:22 ratio and the chiral ligand (*R*,*R*,*R*)-**2**. After repeated chromatographic purifications (SiO_2, hexanes/Et_2O=85:15 plus 1% NEt_3) it was possible to obtain pure **4b** (36 mg) and **6b** (10 mg).

Bicyclo [4.3.0]-2-ethyl-nona-3,5-dien-1-ol (4b): a semisolid; R_f=0.33 (hexanes/Et_2O=85:15); $[\alpha]_D^{23}$=-178.2 (*c*=0.78, MeOH). ^{1}H NMR δ (C_6D_6): 5.84 (dd, 1H, *J* = 9.7 and 5.4 Hz), 5.68-5.54 (m, 2H), 2.51-2.37 (m, 1H), 2.13-1.74 (m, 4H),

1.62-1.44 (m, 2H), 1.42-1.19 (m, 2H), 0.81 (t, 3H, J = 7.2 Hz). ^{13}C NMR δ (C_6D_6): 148.3, 129.1, 123.9, 116.4, 79.3, 46.7, 35.9, 30.5, 24.4, 23.4, 12.2.

Bicyclo [4.3.0]-4-ethyl-nona-2,5-dien-1-ol (6b): a liquid; R_f=0.38 (hexanes/Et_2O=85:15); ^{1}H NMR δ (C_6D_6); 5.96-5.83 (m, 1H), 5.68-5.59 (m, 1H), 5.46 (d, 1H, J = 9.5 Hz), 2.78-2.40 (m, 2H), 2.25-1.96 (m, 4H), 1.87-1.30 (m, 3H), 0.98 (t, 3H, J = 7.4 Hz). ^{13}C NMR δ (C_6D_6): 149.9, 125.1, 116.9, 78.4, 48.5, 40.2, 30.8, 30.1, 23.4, 21.8, 13.0.

Regiodivergent kinetic resolution of naphthalene oxide (8).

Following the typical procedure $Cu(OTf)_2$ (5.8 mg, 0.015 mmol), (*R*,*R*,*R*)-**2** (16.2 mg, 0.03 mmol), arene oxide **8** (144 mg, 1.0 mmol), Et_2Zn (1.4 ml), 3h from –78°C up to –10°C (>98% conversion), afforded after the usual work-up a crude reaction mixture (190 mg) constituted by the regioisomer (1*S*, 4*S*)-**9** and (1*R*, 2*S*)-**10** in a 66:34 ratio (as determined by ^{1}H NMR analysis of the crude reaction mixture) and the chiral ligand (*R*,*R*,*R*)-**2**. Dihydronaphthols **9** and **10** are not separable by chromatography on SiO_2. However it is possible to obtain racemic **9** (isomer **10** < 5%) following the typical procedure employing $Cu(OTf)_2$ (5.8 mg, 0.015 mmol), (*R*,*R*,*R*)(*S*,*S*,*S*)-**2** (16.2 mg, 0.03 mmol), arene oxide **8** (144 mg, 1.0 mmol), Et_2Zn (1.4 ml), 3h from –78°C up to –10°C. The usual work-up afforded a crude reaction mixture (160 mg) containing **9** and **10** in a 97:3 ratio. After chromatographic purification (SiO_2, hexanes/Et_2O=80:20 plus 1% NEt_3) compound **9** (90 mg, 52%) (contaminated with ca. 6% isomer **10**) was obtained.

(±)-4-Ethyl-1,4-dihydronaphth-1-ol (9): ^{1}H NMR δ ($CDCl_3$): 7.69-7.64 (m, 1H), 7.35-7.09 (m, 3H), 6.10-5.92 (m, 2H), 5.04-4.96 (m, 1H), 3.20-3.12 (m, 1H), 1.85-1.63 (m, 2H), 0.62 (t, 3H, J=7.3 Hz). ^{13}CNMR δ ($CDCl_3$): 138.62, 138.27, 131.14, 130.24, 128.11, 127.91, 127.04, 65.62, 40.87, 31.16, 10.46.

All the attempted analyses of the enantiopurity of alcohol **9** both by HPLC- and GC-CSPs gave extensive decomposition of the compound.

(+)-(1*R*, 2*S*)-2-Ethyl-1,2-dihydronapht-1-ol (10): ^{1}H NMR δ ($CDCl_3$): 7.39-7.11 (m, 4H), 6.51 (d, 1H, *J*=10.0 Hz), 6.01 (dd, 1H, *J*=9.5 and 4.6 Hz), 4.40 (d, 1H, *J*=4.7 Hz), 2.53-2.47 (m, 1H), 1.59-1.26 (m, 2H), 0.97 (t, 3H, *J*=7.3 Hz). ^{13}CNMR δ ($CDCl_3$): 136.44, 133.04, 131.42, 129.13, 128.38, 128.29, 127.14, 126.75, 72.77, 44.72, 25.18, 12.20. The enantiomeric excess of **10** (>98%) was determined at 254 nm by chiral HPLC (Daicel Chiralcel OD-H column), hexanes / 2-propanol 96:4, flow rate 0.5 mL/min, (-) t_R15.0, (+) t_R 16.5 min.

The absolute configuration of compound (1*R*, 2*S*)-**10** was demonstrated by a single crystal X-ray analysis after derivatization of the enantiomer (1*S*, 2*R*)-**10** with a chiral auxiliary derived from 4,5-dichlorophthalic acid and (1*S*,2*R*,4*R*)-(-)-2,10-camphorsultam.[2]

[2] [2] N. Harada,N. Koumura, M. Robillard. *Enantiomer* 1997, ***2***, 303